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Pesticide Fact Sheet Number 202: Flurprimidol

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This document contains up-to-date chemical information, including a summary of the Agency's regulatory position and rationale, on a specific pesticide or group of pesticides. A Fact Sheet is issued after one of the the following actions has occurred.

1. Issuance or reissuance of a registration standard,
2. Issuance of each special review document,
3. Registration of a significantly changed use pattern,
4. Registration of a new chemical, or
5. An immediate need for information to resolve controversial issues relating to a specific chemical or use pattern.

17. Document Analysis a. Descriptors

Pesticides, regulations, Chemical Information Fact Sheet, Use Patterns, science findings.

b. Identifiers/Open-Ended Terms

c. COSATI Field/Group

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Office of Pesticides and Toxic Substances
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Washington, DC 20460

540/FS-89-054

EPA

Pesticide Fact Sheet

Name of Chemical: Flurprimidol
Reason for Issuance: New Chemical Registration
Date Issued: FEB 22 1989
Fact Sheet Number: 202

DESCRIPTION OF CHEMICAL

Generic Name: alpha-(1-methylethyl)-alpha-[4-(trifluoromethyoxy) phenyl]-5-pyrimidinemethanol

Common Name: Flurprimidol

Trade Name: Cutless

EPA Shaughnessy Codes: 125701-3

Chemical Abstracts Service (CAS) Number: 56425-91-3

Year of Initial Registration: 1989

Pesticide Type: Plant Growth Regulator

U.S. and Foreign Producers: Elanco Products Company, Division of Eli Lilly and Company

USE PATTERNS AND FORMULATIONS

Application Sites: Turfgrasses and ornamental trees

Types and Methods of Application:

Boom-type sprayer to turfgrasses and specialized injection equipment to ornamental trees.

Application Rates:

50% wettable powder:

Cool season turfgrasses
Late Spring - Early Summer 1.5 - 3 lbs./ai/A
Late Summer - Early Fall 1.5 - 3 lbs./ai/A

Warm season turfgrasses
Late Spring - Early Summer 0.75 - 3 lbs./ai/A
Late Summer - Early Fall 0.75 - 3 lbs./ai/A

Poa annua
Late Spring - Early Summer 1 - 1.5 lbs./ai/A
Late Summer - Early Fall 1 - 1.5 lbs./ai/A

99% technical powder:

Ornamental trees - 0.5 - 1.50 grams per inch tree diameter

Types of Formulations:

50% wettable powder (WP) end-use product marketed in water soluble packets and 99% technical powder (TP) end-use product marketed in one quart bottles.

Major Uses:

Turfgrasses: End-use formulation is a plant growth regulator which reduces internode and leaf elongation in cool and warm season turfgrasses.

Ornamental trees: End-use formulation is a plant growth regulator for reduction of growth and pruning frequency.

Usual Carrier:

50% formulation - water
99% formulation - alcohol

SCIENCE FINDINGS

Summary Science Statement:

Chronic feeding/oncogenicity studies were conducted in both the rat and mouse. Hepatocellular changes in the males including enzyme induction, fatty change, hepatocellular eosinophilic change and focal atypia were observed in the rat study. A core-supplementary mouse study showed increased absolute and relative liver weight in females. Although both the rat and mouse study are core-supplementary for oncogenicity due to inadequate dose selection, they both satisfy the requirement for oncogenicity testing in one species for the requested non-food uses. No oncogenic potential was observed at any dose level in either of these two studies. New rat and mouse studies (which achieve the Maximum Tolerated Dose - MTD) will be required for any food use registrations.

A 1-year dog study showed adrenal changes including decreased plasma cortisol response to adrenal cortico-tropine hormone (ACTH) stimulation (males), decreased relative

and absolute adrenal weight (males) and degenerative changes of the adrenal cortex (males and females). This study satisfies the requirement for a chronic oral study in one species.

Decreased body weight and food consumption were observed in the rabbit and rat teratology studies. In addition the rat teratology study showed increased mortality, stained perigenital area and snout, chromodacryorrhea, decreased muscle tone, hypoactivity and alopecia. Rat and rabbit teratology requirements have been satisfied.

The requirements for a 90-day feeding study have been satisfied. A subchronic oral rat study showed an increased hepatic enzyme induction in males (significant and dose increases in p-nitroanisol o-demethylase activity). The subchronic oral mouse study indicated an increased incidence of hepatocellular hypertrophy in the males.

A 21-day dermal toxicity study (rabbit) noted slight transient dermal irritation. This data requirement has been fulfilled.

The requirements for a 2 generation reproductive study have been satisfied. The Parental Systemic Toxicity in a 2 generation reproduction study showed increased incidence of non-neoplastic hepatocellular alteration including fatty change and vacuolation (males) and increased susceptibility to stress factors. Decreased mating, fertility, fetal survival (stillbirths), neonatal survival and neonatal body weight in both sexes and in both generations were observed at the Reproductive NOEL. Other parental signs of toxicity included increased susceptibility to stress (pregnant females) resulting in death, increased relative liver weight (males and females), depressed body weight, weight gain and food consumption (males and females).

Subchronic, oncogenicity and teratogenicity studies are not usually required for the requested registration use patterns. However, due to the structural similarity of flurprimidol to compounds of toxicological concern (fenarimol, triarimol, and nuarimol), these studies were required for registration. Oncogenicity studies were requested based on flurprimidol's similarity to an oncogenic compound (triarimol) and teratogenicity studies were requested based on it's similarity to compounds (triarimol and fenarimol) associated with developmental concerns.

Mutagenicity tests for gene mutation, chromosomal aberration and direct DNA damage were evaluated. Flurprimidol had no effect on induction of unscheduled DNA synthesis or chromosomal aberration. It was also negative for mutagenic activity.

The hydrolysis, aerobic and anaerobic soil metabolism, leaching and adsorption/desorption, terrestrial field dissipation, and accumulation studies are acceptable and fulfills the data requirements for proposed turf use. Environmental fate data demonstrates that flurprimidol is stable and moderately mobile. Based upon evaluation of the environmental fate data for the currently proposed uses, the Ground Water Team recommends no prospective ground water monitoring study be required. A study may be required if the use of the chemical is expanded to terrestrial food crops.

The aqueous photodegradation study is considered less than adequate by itself to support registration. However, when evaluated with other acceptable photolysis studies on chemicals of the same class, these data demonstrate a degradation pathway consistent with other studies. This study is not required for the proposed tree injection use. As such, this data requirement is satisfied for turf use since the chemical dissipates rapidly on turf. However, in the case of bare loam soil where crops are generally grown, the chemical may not dissipate rapidly and is therefore subject to photodegradation. Accordingly, a repeat photodegradation study is required for future (food) uses of flurprimidol.

Avian acute, avian dietary, freshwater fish, freshwater invertebrate and acute contact toxicity studies have been fulfilled. Studies indicate that flurprimidol is slightly toxic to birds, aquatic invertebrates, and both warmwater and coldwater species.

Chemical Characteristics of the Technical Material

Physical State: crystalline solid

Color: buff to off-white, white to pale yellow

Odor: none - slightly aromatic

Molecular Weight: 312.3

Empirical Formula: $C_{15}H_{15}F_3N_2O_2$

Boiling Point: 264 degrees Celsius

Melting Point: 93 to 95 degrees Celsius

Vapor Pressure: 3.64×10^{-7} mmHg @25 degrees Celsius

Density: 0.83 to 0.88 g/cc

Octanol/Water Partition Coefficient: K_W = 9.33

pH: In D-H_2O 6.5 to 8.9

Solubility in various solvents:

water, pH 4	120 to 140 ppm @25 degrees Celsius
water, pH 7	120 to 140 ppm @25 degrees Celsius
water, pH 10	120 to 140 ppm @25 degrees Celsius
Acetone	*700 to 800 mg/mL
Acetonitrile	*200 to 300 mg/mL
Toluene	*75 to 100 mg/mL
Chloroform	*800 to 900 mg/mL
Dichloromethone	*800 to 900 mg/mL
Methanol	*700 to 800 mg/mL
Heavy Aromatic Naphtha	*25 to 35 mg/mL
Xylene	*100 to 200 mg/mL
1-Chlorobutane	*100 to 200 mg/mL
n-Hexane	*1 to 2 mg/mL
Methyl Cellosolve	*700 to 800 mg/mL
Cyclohexane	*2 to 3 mg/mL
Ethyl Acetate	*500 to 600 mg/mL
Cyclohexane	*400 to 500 mg/mL
Isophorone	*400 to 500 mg/mL
Acetophenone	*400 to 500 mg/mL
Monochlorotoluene (90% ortho, 10% para)	*400 to 500 mg/mL

*Solubilities determined at ambient temperature, 20 to 22 degrees Celsius.

Stability: Stable in glass or polyethylene container

Oxidizing or Reducing Action:

Oxidizing or reducing action reagent: Ammonium dihydrogen phosphate - no gas evolution, no temperature rise over 24 hours.

Reagent: Potassium permanganate - no gas evolution, no temperature rise over 24 hours.

Reagent: Zinc dust 100 mesh - no gas evolution, no temperature rise over 24 hours.

Corrosion Characteristics:

Not corrosive to low density polyethylene films and high density polyethylene containers.

Explodability:

No positive results were obtained in 10 repetitive drops at 20 inches with an eight pound hammer.

Toxicology Characteristics

Acute Studies

Acute Oral Toxicity: Toxicity Category III
Rat: LD_{50} 914 mg/kg (male)
LD_{50} 709 mg/kg (female)

Acute Dermal Toxicity: Toxicity Category III
Rat: LD_{50} > 500 mg/kg (male and female)

Primary Dermal Irritation: Toxicity Category IV
Slight dermal irritant

Primary Eye Irritation: Toxicity Category III
Moderate eye irritant

Dermal Sensitization:
Not a sensitizer

Acute Inhalation: Toxicity Category IV
Rat: LD_{50} > 5.231 mg/L (male and female)

The toxicity base for the technical product supports registration of this compound for the requested uses.

Subchronic Studies

A 90-day feeding study in rats treated to 0, 1.68, 6.04, 20.39, 68.34 mg/kg/day (males) and 0, 1.98, 7.13, 24.37, 78.47 mg/kg/day (females) of flurprimidol. The systemic No-Observable-Effect-Level (NOEL) was 1.68 mg/kg/day and the Lowest-Effect-Level (LEL) was 6.04 mg/kg/day based on increased hepatic enzyme induction in males (significant and dose increases in p-nitroanisol 0-demthylase activity). At 24.37 mg/kg/day there was increased relative and absolute ovarian (female) and relative liver (male) weight. At 68.34 mg/kg/day, there was increased absolute liver weight (males).

A 90-day feeding study in the mouse, treated with 0, 15, 67.5 and 300 mg/kg/day of technical flurprimidol. The NOEL was 15 mg/kg/day and the LEL was 67.5 mg/kg/day based on increased

incidence of hepatocellular hypertrophy in the males. At 300 mg/kg/day, there was evidence of enzyme induction, increased liver weight and hepatocellular hypertrophy in females.

A subchronic dermal study (21-day) was conducted in the rabbit. Groups of 5 rabbits/sex/group were treated by dermal exposure to 0, 500, or 1000 mg/kg/day of flurprimidol. The systemic NOEL was greater than or equal to 1000 mg/kg/day and the LEL was greater than 1000 mg/kg/day. The NOEL for dermal irritation was less than 500 mg/kg/day and the LEL was less than or equal to 500 mg/kg/day based on slight transient dermal irritation.

Chronic Studies

Rodent Feeding Studies

A 2-year study in rats treated with either 0, 1.0, 3.6, 12.1 and 41.2 mg/kg/day of flurprimidol technical for males and 0, 1.2, 4.4, 14.5, and 49.3 mg/kg/day for females the NOEL was 3.6 mg/kg/day and the LEL was 12.1 mg/kg/day based upon hepatocellular changes in males including enzyme induction, fatty change, hepatocellular eosinophilic change and focal atypia. At 41.2 mg/kg/day there was also a transient body weight and weight gain decrease (males), increased cholesterol and triglycerides (males and females) increased hepatic enzyme induction and liver weight, fatty change and hepatocellular eosinophilic change (females). No oncogenic potential was observed at any dose level.

A 2-year core-supplementary study in mice treated with either 0, 1.4, 10.5 or 79.9 mg/kg/day of flurprimidol, the systemic NOEl was 1.4 mg/kg/day. The LEL was 10.5 mg/kg/day based on increased absolute and relative liver weight in the males. No oncogenic potential was observed at any dose level.

Although both the rat and the mouse study are supplementary for oncogenicity due to inadequate dose selection, they both satisfy the requirement for oncogenicity testing in one species for the requested non-food use. There was no indication of oncogenic potential at any dose level in either study.

New rat and mouse studies will be required for any food use registrations.

Non-rodent Feeding Study

A 1-year dog study treated with flurprimidol at doses of 0, 0.5, 1.5, 7.0 and 30.0 mg/kg/day, the NOEl was 7.0 mg/kg/day and

the LEL was 30.0 mg/kg/day Highest Dose Tested (HDT) based on adrenal changes including decreased plasma cortisol response to ACTH stimulation (males and degenerative changes of the adrenal cortex (males and females). The histopathology was limited to the zona fasciculata of the adrenal cortex and was characterized by eosinophilic degeneration, vacuolation and cortical atrophy. There was a slight increase in hepatic p-nitroanisole o-demethylase activity (males).

Teratology Studies

A rabbit teratology study using doses of 0, 1.7, 9 and 45 mg/kg/day of flurprimidol had a maternal toxicity NOEl of 9 mg/kg/day and the LEL was 45 mg/kg/day based on decreased body weight and food consumption.

A rat teratology study using doses of 0, 2.5, 10, 45 or 200 mg/kg/day of flurprimidol had a maternal toxicity NOEL of 10 mg/kg/day and a LEL of 45 mg/kg/day based on decreased body weight gain and food consumption. The developmental NOEL was 10 mg/kg/day and the LEL was 45 mg/kg/day based on decreased fetal weight, increased incidence of hydronephrosis, hydroureter and numerous developmental skeletal anomalies.

Reproduction Study

A 2 generation reproduction study in the rat treated with (time weighted average) 0, 1.8, 7.3, and 74 mg/kg/day of flurprimidol had a Parental Systemic Toxicity NOEL of 1.8 mg/kg/day and a LEL of 7.3 mg/kg/day based on increased incidence of non-neoplastic hepatocellular alterations including fatty change and vacuolation (males) and increased susceptibility to stress factors. The Reproductive NOEL was 7.3 mg/kg/day and the LEL was 74 mg/kg/day based on decreased mating, fertility, fetal survival (stillbirths), neonatal survival and neonatal body weight in both sexes and in both generations. There was an increased incidence of persistent vaginal estrous and no corpora lutea. Additional parental signs of toxicity at 74 mg/kg/day included increased susceptibility to stress (pregnant females) resulting in death, increased relative liver weight (males and females), depressed body weight, weight gain and food consumption (males and females).

Mutagenicity Studies

No mutagenic activity was observed in mammalian cells. There was also no activity when tested in S. typhimurium and E. coli. Flurprimidol did not induce chromosome aberrations in

vitro in Chinese Hamster ovary cells. There was no effect on the capacity to induce sister chromatid exchanges in bone marrow cells of Chinese Hamsters. It had no effect on induction of unscheduled DNA synthesis in rat hepatocytes.

Mutagenicity tests for gene mutation, chromosomal aberration and DNA repair were negative.

Environmental Characteristics

Hydrolysis
stable at pHs 5,7, and 9

Aerobic Soil Metabolism
degrades with a half-life of > 26 weeks in sandy loam, silt loam and clay loam soils.

Mobility
Mobile in bare loam soil

Dissipation
persistent in unvegetated loam (estimated half-life of 1.5 years)

dissipates rapidly on turf (half-life of 5-21 days)

Accumulation
displays a low bioconcentration factor in fish with rapid depuration.

The Environmental Fate and Ground Water Branch (EFGWB) have concluded that the hydrolysis, aerobic and anaerobic soil metabolism, leaching and adsorption/desorption, terrestrial field dissipation, and accumulation studies are acceptable and fulfills the data requirements for proposed turf use.

Review of the Aqueous Photodegradation study noted several deficiencies. The study is considered less than adequate by itself to support registration. However, when evaluated with other acceptable photolysis studies on chemicals of the same class, these data demonstrate a degradation pathway consistent with the other studies. This study is not required for the proposed tree injection use. As such, this data requirement is satisfied for turf use since the chemical dissipates rapidly on turf. However, in the case of bare loam soil where crops are generally grown, the chemical may not dissipate rapidly and is therefore subject to photodegradation. Accordingly, a repeat photodegradation study is required for future (food) uses of flurprimidol.

A repeat of the Aqueous Photodegradation study is requested, but not as a condition of registration. A new study will remove any doubt concerning the data and the available study submitted by the registrant is a passe' protocol. Without a free standing study, the question of acceptability will continually arise with every new use and generic review of the chemical.

Ecological Characteristics

Avian acute toxicity:	
bobwhite quail	LC_{50} > 2000 mg/kg
Avian dietary toxicity:	
bobwhite quail	LC_{50} > 5000 ppm
mallard duck	LC_{50} > 5000 ppm
Freshwater fish acute toxicity:	
bluegill sunfish	LC_{50} 17.2(16.6 and 17.8) ppm
rainbow trout	LC_{50} 18.3(17.5 and 19.0) ppm
Freshwater invertebrate toxicity:	
Daphnia magna	EC_{50} 11.8(10.9 and 12.9) ppm
Acute Toxicity for Green Algae:	
Selenastrum capricornutum	EC_{50}.84 ppm
Acute Contact Toxicity:	
honey bee	LD_{50} > 100 ug/bee

All of the above data requirements have been satisfied. Flurprimidol is practically non-toxic to birds on an acute and dietary basis, slightly toxic to aquatic invertebrates, and both warmwater and coldwater species. The hazard to freshwater algae is expected to be minimal. In addition flurprimidol is relatively non-toxic to honey bees.

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DISCLAIMER: The information in this Pesticide Fact Sheet is a summary only and is not to be used to satisfy data requirements for pesticide registration and reregistration. The complete Registration Standard for the pesticide may be obtained from the contact person listed above.